REMARKS

I. OVERVIEW

Claims 73-75 and 83-84 and 98-104 are currently pending in this application. Claims 102-104 have been canceled. The present response is an earnest effort to place all claims in proper form for immediate allowance. Reconsideration and passage to issuance is therefore respectfully requested.

II. CLAIM REJECTIONS - 35 U.S.C. § 112

Claims 73-75, 83-84 and 98-101 remain rejected and claims 102-104 have been rejected under 35 U.S.C. § 112, first paragraph because the Examiner states that the specification, while being enabling for the transgenic plants expressing the specific animal viral antigens at the level set forth in Applicant's working examples, does not reasonably provide enablement for expressing in all plants recombinant viral antigen proteins obtained from all animal viruses.

Examiner maintains the rejections on the belief that the expression of two different recombinant viral antigen proteins at the desired levels in transgenic plants as exemplified in the instant application does not provide sufficient guidance with respect to how one may express a multitude of structurally and distinct animal viral antigen proteins at the desired levels. Office Action, March 17, 2004, at page 3. The Examiner also argues "the recitation in the specification of a multitude of known animal viral antigen proteins does not provide sufficient guidance with respect to how one may express these structurally and functionally distinct animal viral antigen proteins at the desired levels in transgenic plants." Office Action, March 17, 2004, at page 3.

The Examiner states that the type of promoter used and stability of expressed mRNA are variables that are unpredictable and one does not know how to express a variety of viral antigens. However, Applicants are not required to teach what is well known in the art. *Hybritech, Inc. v Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986). One skilled in the art would know how to express a variety of viral antigens. The present invention is directed to transgenic plants and is not tied to a particular method for producing the plants or to a particular promoter for expressing foreign proteins as Examiner seems to suggest. The instant Specification teaches, at pages 11-12 and 19-20, that

> [t]he methods of the invention provide for any of a number of transformation protocols in order to transform the plant cells and plants of the invention. While certain preferred embodiments described below utilize particular transformation protocols, it will be understood by those of skill in the art that any transformation method may be utilized with in the definitions and scope of the invention. Such methods include microinjection, polyethylene glycol mediated uptake, and electroporation. Thus, certain preferred methods will utilize an *Agrobacterium* transformation system, in particular, where the *Agrobacterium* system is an *Agrobacterium tumefaciens*-Ti plasmid system. In other preferred methods, the plant cell is transformed utilizing a microparticle bombardment transformation system.
>
> ... plasmid vectors for transforming a plant are claimed comprising a DNA sequence encoding a mammalian viral immunogen and a plant-functional promoter operably linked to the DNA sequence capable of directing the expression of the immunogen in said plant.
>
> Promoters which are known or found to cause transcription of a foreign gene in plant cells can be used in the present invention. Such promoters may be obtained from plants or viruses and include, but are not necessarily limited to: the 35S promoter of cauliflower mosaic virus (CaMV) (as used herein, the phrase "CaMV 35S" promoter includes variations of CaMV 35S promoter, e.g. promoters derived by means of ligations with operator regions, random or controlled mutagenesis, etc.); promoters of seed storage protein genes such as Zma10Kz or

> Zmag12 (maize zein and glutelin genes, respectively), light-inducible genes such as ribulose bisphosphate carboxylase small subunit (rbcS), stress induced genes such as alcohol dehydrogenase (Adh1), or "housekeeping genes" that express in all cells (such as Zmaact, a maize actin gene)..sup.4, 55 This invention can utilize promoters for genes which are known to give high expression in edible plant parts, such as the patatin gene promoter from potato...sup.56

The *Agrobacterium*-mediated transformation method was well known those of skill in the art at the time the application was filed. Nonetheless, Applicants have described this method in detail. Specification, at pages 18-19. Furthermore, the Federal Circuit has held "[t]he enablement requirement is met if the description enables any mode of making and using the claimed invention." *Engel Industries Inc. v. The Lockformer Co.*, 20 USPQ2d 1300, 1304 (Fed. Cir. 1991). The present invention clearly meets this requirement as it provides working examples of transgenic plants that are genetically modified to express animal viral antigen proteins. Specification, Examples 1-3. Accordingly, there is no prima facie case showing that the claimed invention is not enabled.

Thus, the specification directs one skilled in the art to use the tools already available in practicing the invention of expressing vaccine antigens in plants. A multitude of promoters was known to one skilled in the art, in addition to those examples listed in the specification. For example: the ubiquitin promoter (European patent application no. 0 342 926); the promoter for the small subunit of ribulose-1,5-bis-phosphate carboxylase (ssRUBISCO) (Coruzzi, et al., EMBO J., 3:1671, 1984; Broglie, et al., Science, 224:838, 1984), or promoters from the tumor-inducing plasmids from *Agrobacterium tumefaciens,* such as the nopaline synthase and octopine synthase promoters (carried on tumor-inducing plasmids of *Agrobacterium tumefaciens* and have plant activity); the figwort mosaic virus 35S promoter(Gowda, et al., J. Cell Biochem., 13D: 301,

1989) or the coat protein promoter of TMV (Takamatsu, et al., EMBO J. 6:307, 1987; the mannopine synthase promoter (Velten, et al., EMBO J., 3:2723, 1984); heat shock promoters, e.g., soybean hspl7.5-E or hspl 7.3-B (Gurley, et al., Mol. Cell. Biol., 6:559, 1986; Severin, et al., Plant Mol. Biol., 15:827, 1990); or ethanol-inducible promoters (Caddick et al., Nature Biotech., 16:177, 1998). Can one achieve successful expression of viral antigens in plants using what is taught in the specification? Indeed, following the precise teachings of the specification has resulted in viral antigen expression. Wigdorovitz et al, (See Wigdorovitz et al. 1999 Virology 264, 85-91 presented in amendment of April 19, 2003 in the parent application), used 35S and *Agrobacterium* transformation to express the VP1 gene in alfalfa.

In addition, Applicants have submitted for Examiner's consideration five published journal articles authored by one of the inventors wherein methods disclosed in the present application were successfully employed to produce transgenic plants that express foreign proteins. These journal articles are presented in direct response to the Examiner's statement where she states for the first time in the final rejection that the additional examples are not supportive because of using different particular components. The new articles show that even if the different components are not used, one can follow the invention and achieve results, and further the arguments rebut that variations were not known to one skilled in the art. For example, Arntzen et al. describes the expression of the recombinant Norwalk virus capsid protein (NVCP) to produce a transgenic *Solanim tuberosum* L. (potato) plants expressing the NVCP protein. Tacket CO, Mason HS, Losonsky G, Estes MK, Levine MM, Arntzen CJ. Human Immune Responses to a Novel Norwalk Virus Vaccine Delivered in Transgenic Potatoes. J INFECT DIS. 2000. 182(1):302-5. To produce this protein in plants, the CTB gene, linker and P1 peptide sequences were PCR assembled and ultimately cloned into the plant expression vectors driven by

the Ca35S cauliflower mosaic virus (CaMV35S) promoter. The transgenic potatoes were found to contain as much as ~538 and 751 μg of NVCP per 150-g dose. J INFECT DIS., at page 303.

Similarly, Arntzen et al describe using *Agrobacterium*-mediated transformation of *Musa* ssp. var. Grand Nain to generate transgenic bananas expressing the kanamycin resistance gene (NPT) and the enzyme β-glucuronidase (GUS). May, G.D., R. Afza, H.S. Mason, A. Wiecko, F.J. Novak and C.J. Arntzen. Generation of Transgenic Banana (*Musa acuminata*) Plants Via *Agrobacterium*-mediated Transformation. BIO/TECHNOLOGY 1995. 13:486-492. The NPT and GUS genes were cloned into a plasmid with their expression being driven in the banana by the NOS promoter and rice actin promoter respectively. BIO/TECHNOLOGY, at page 490 and 491. Van Eck et al describes the use of the *Agrobacterium*-mediated transformation to make transgenic *Musa* ssp. Rasthali cultivar that express GUS as driven by the Gelvin promoter. Ganapathi, T.R., Higgs, N.S., Balint-Kurti, P.J., Arntzen, C.J., May, G.D., Van Eck, J.M. *Agrobacterium*-mediated Transformation of Embryogenic Cell Suspensions of the Banana Cultivar Rasthali (AAB). PLANT CELL REPORTS. 2001. 20:157-162, at page 159.

Mason et al describe using *Agrobacterium*-mediated transformation of tomato to generate transgenic tomatoes expressing the B subunit of *E. coli* heat labile enterotoxin. Walmsley AM, Alvarez ML, Jin Y, Kirk DD, Lee SM, Pinkhasov J, Rigano MM, Arntzen CJ, Mason HS. Expression of the B Subunit of Escherichia coli Heat-labile Enterotoxin (LTB) as a Fusion Protein in Transgenic Tomato. PLANT CELL REP. 2003. 21(10):1020-6. The LTB sequence was cloned into a plasmid with LTB expression being driven in the tomato by the CaMV 35S promoter and the TEV 5'UTR of the tobacco etch virus. PLANT CELL REP., at page 1021. Additionally, Arntzen et al describe the successful expression of LTB in both tobacco and potato

plants. Haq TA, Mason HS, Clements JD, Arntzen CJ. Oral Immunization with a Recombinant Bacterial Antigen Produced in Transgenic Plants. SCIENCE. 1995. 268(5211):714-6.

There is no evidence that one of skill in the art would consider the *Agrobacterium*-mediated transformation method or selection and use of varying promoters to express a foreign protein in a plant to be undue experimentation. Rather, the published journal articles show that varying methods and promoters for generating transgenic plants have been successfully employed to create a number of transgenic plants expressing diverse foreign proteins.

Accordingly, the published journal articles demonstrate that one of skill in the art, relying on the present disclosure and on knowledge in the art at the time the present application was filed, would be able to produce a variety of transgenic plants capable of expressing different animal viral antigen proteins. Accordingly, the Specification and published articles demonstrate that the methods of the invention are enabled for expressing different animal viral antigen proteins.

The Examiner rejects the two examples provided in the last action showing successful expression in plants of HIV-related proteins (US20040061) and expression of fish antigens VP2 and VP3 proteins in plants (US20040175441). The Examiner states these examples do not follow the teachings of the invention because the sequences used were (1) codon optimized for maize, (2) linked to a barley alpha amylase secretion signal (3) had a PinII terminator sequence and 4) used a pGNpr2 promoter sequence. The Examiner says this does not follow the method shown of using a patatin promoter sequence and NOS polyadenylation sequence or a 35S promoter or 35S dual promoter with a NOS polyadenylation sequence, as shown in the examples in the specification.

However, the specification makes it clear that the invention is not limited to those examples. As noted above, it discusses that one skilled in the art appreciates that variations in components are available. The pGNpr4 promoter sequence used in the fish antigen and HIV related surface protein is an ubiquitin-like promoter, ubiquitin promoters having been well known in many variations for some time (see for example, WO 01/94394). The barley alpha amylase signal sequence has been known and used since 1985. Rogers, J. Biol. Chem. 260:3731-3738 (1985). The pinII terminator is one of a variety of terminators one can choose from, and also is a component one skilled can elect to use, known since 1989. An et al., *Plant* Cell 1:115-122 (January 1989). Also known is the use of codon optimization for increasing expression in a particular plant. See, Campbell and Gowri (1990) *Plant Physiol.* 92:1-11 for a discussion of host-preferred codon usage as well as U.S. Patent Nos. 5,380,831, 5,436,391, and Murray *et al.* (1989) *Nucleic Acids Res.* 17:477-498.

Can one achieve viral antigen expression using the teachings of the invention? The journal articles demonstrate the answer is yes. Can one achieve even higher expression using various other components? That is also possible. Those following the general and precise teachings of the specification of the invention can and have achieved expression of viral antigens in plants.

These examples demonstrate what the present invention taught for the first time; one can express viral antigens in plants. This has been recognized by scientists in the field, including Wigdorovitz et al, who in 1999 acknowledged Mason et al to be the first to teach one how to express viral antigens in plants as well as Gomez in 1998. (See Wigdorovitz et al. 1999 Virology 264, 85-91 presented in amendment of April 19, 2003 in the parent application to the present

filing and Gomez et a1998 Virology 249, 352-358, presented in December 15, 2003 amendment in parent application).

In light of the above arguments, Applicants submit that the grounds for the section 112 rejection has been overcome. The claims of the present invention are fully enabling and commensurate in scope with the disclosure of the claimed invention. Therefore, Applicants request that the rejections under 35 U.S.C. § 112 be withdrawn.

III. DOUBLE PATENTING

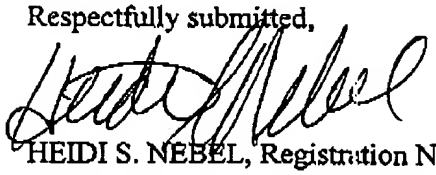
The Examiner states that claims 102-104 stand rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over claim 8 of U.S. Patent No. 6,136,320, claims 1-3 of U.S. Patent No. 6,034,298, claims 1-7 of U.S. Patent No. 5,914,123, and claims 5-14 of U.S. Patent No. 5,484,719. Applicants will be pleased to address this rejection once the Examiner has indicated that the present claims are allowable.

IV. CONCLUSION

This is a request under the provision of 37 CFR § 1.136(a) to extend the period for filing a response in the above-identified application for one month from March 2, 2005 to April 2, 2005. Applicant is a small entity; therefore, please charge Deposit Account number 26-0084 in the amount of $60.00 for one month to cover the cost of the extension. Any deficiency or overpayment should be charged or credited to Deposit Account 26-0084. No additional fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,



HEIDI S. NEBEL, Registration No. 37,719
McKee, Voorhees & Sease, P.L.C.
801 Grand Avenue, Suite 3200
Des Moines, Iowa 50309-2721
Phone No. (515) 288-3667
Fax No. (515) 288-1338
CUSTOMER NO: 22885

-pw- Attorneys of Record